CBER Warning Letters

The Orange County Regulatory Affairs (OCRA) Discussion Group
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Irvine, California

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Warning Letters

- Informal advisory - no legal responsibility to issue warning
- States agency's position, but does not require the agency to take enforcement action
- Require a company response
- Other government agencies notified
- Posted on the website
- Inadequacies in your FDA-Form 483 response will be addressed
- Usually FDA's last attempt to get company's attention before enforcement action

Types of Warning Letters: CBER/OCBQ

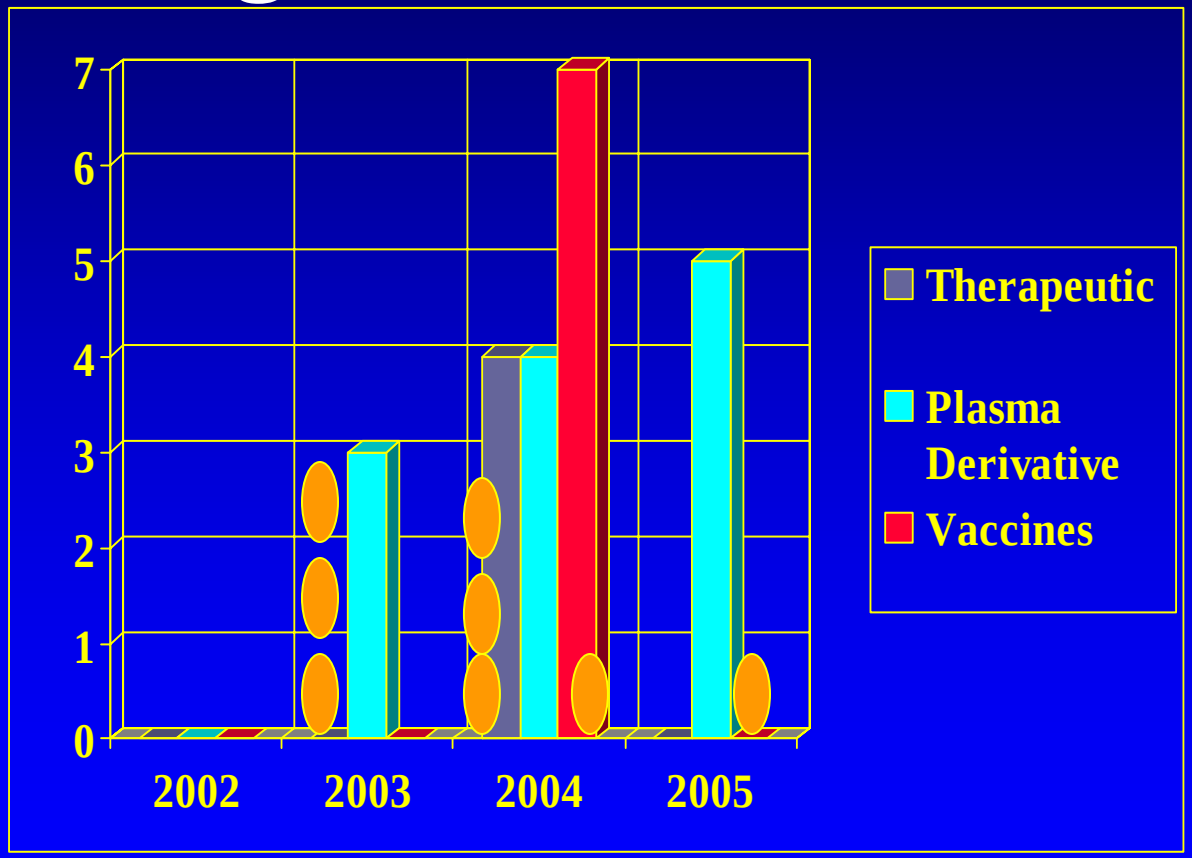
- CBER/OCBQ issues Warning Letters for violative:
  - Advertising and Promotional labeling
  - Bioresearch Monitoring (BIMO) – GCP, GLP, GMP
  - Unapproved biological drugs and devices from all sources, e.g. Internet surveillance, complaints
- CBER/OCBQ reviews Warning Letter recommendations from ORA for:
  - All CBER products inspected by Team Biologics
  - Human Cell and Tissue Products (HCT/Ps)
  - Certain blood and plasma violations

Most Common Violations

- **Advertising and Promotional Labeling**
  - **Discussion of benefits/efficacy with omission of risk information and/or adequate directions for use [21 CFR 201.100(d)**
  - **Failure to submit to FDA at the time of dissemination [21 CFR 601.12(f)(4)]**
- **BIMO**
  - **Failure to protect subjects and/or to follow the investigational protocol [21 CFR 312.66 or 812.100]**
  - **Lack of IRB review and approval [21 CFR 312.66]**

C B
E R

Advertising and Promotional Labeling Branch (APLB) Warning and Untitled Letters



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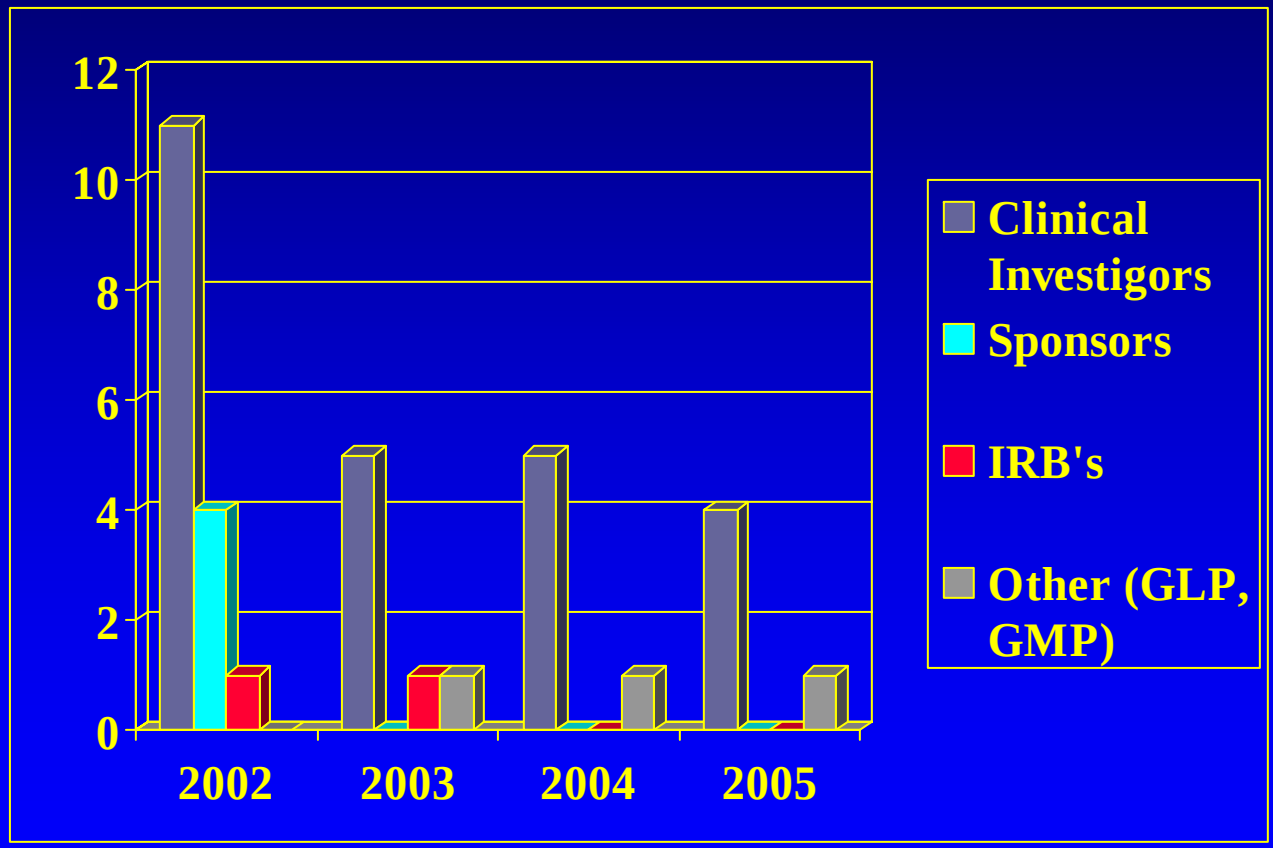
Warning Letters
BIMO



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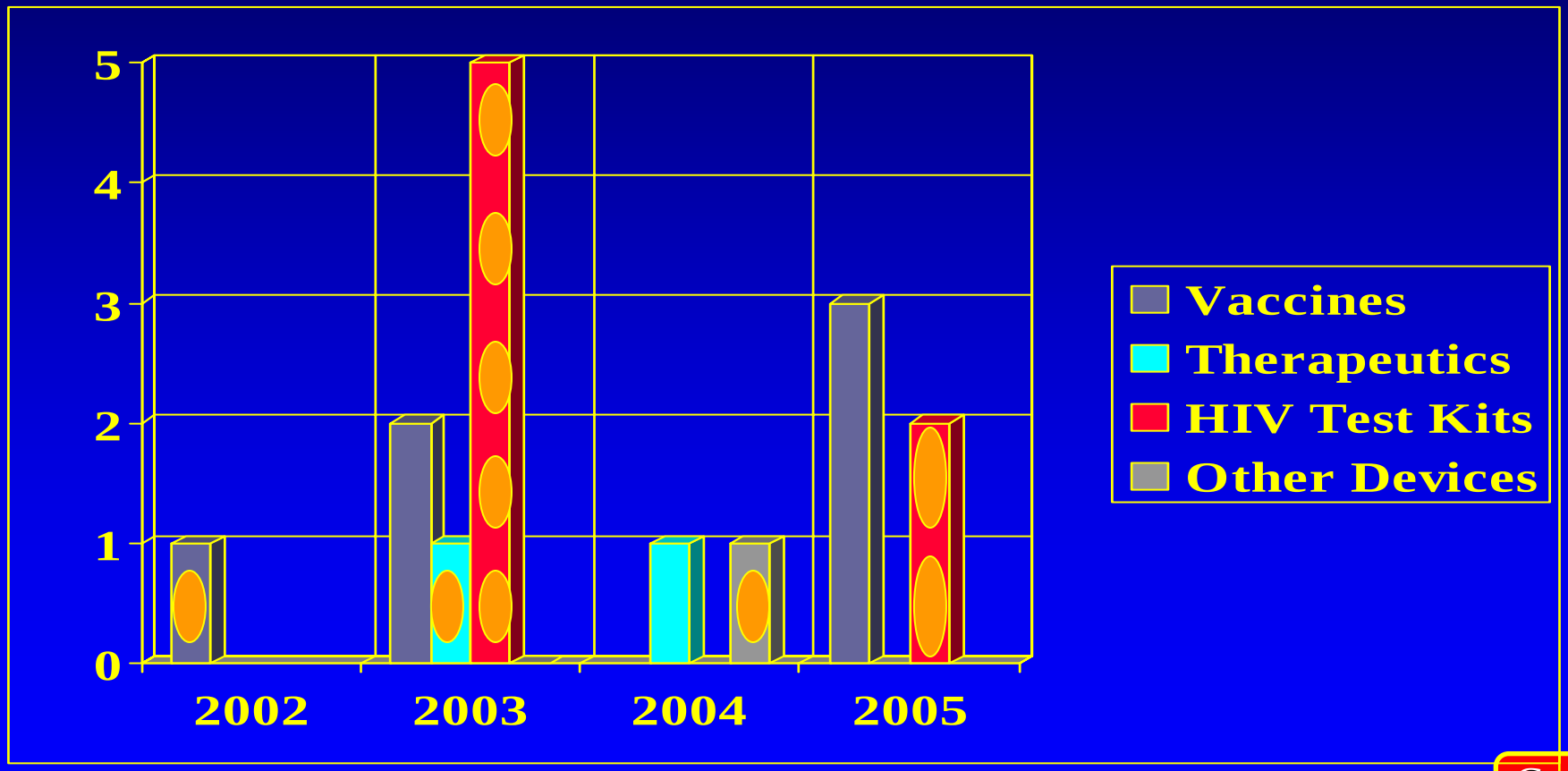
Most Common Violations

- **Unapproved products**
  - **Offering products for sale in interstate commerce that meet the definition of a biological drug or device and are not approved by FDA or under an IND or IDE:**
  - **Most frequent:**
    - **“vaccines” against counter terrorism agents**
    - **“miracle” biological drugs**
    - **HIV home test kits**

Internet
Warning and Untitled Letters



Untitled Letters

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Most Common Violations

- **Biological drug GMPs**
  - **Lack of or inadequate investigation into unexplained discrepancies/deviations/failures, coupled with lack of quality oversight [21 CFR 211.192/21 CFR 211.22]**
- **Biological device QSR**

Inadequate Correction and Preventive actions (CAPA) [21 CFR 820.100]

- **Inadequate design controls [21 CFR 820.30]**
- **Lack of management responsibility [21 CFR 820.20]**

- **Consistent with other drug and device WLs**

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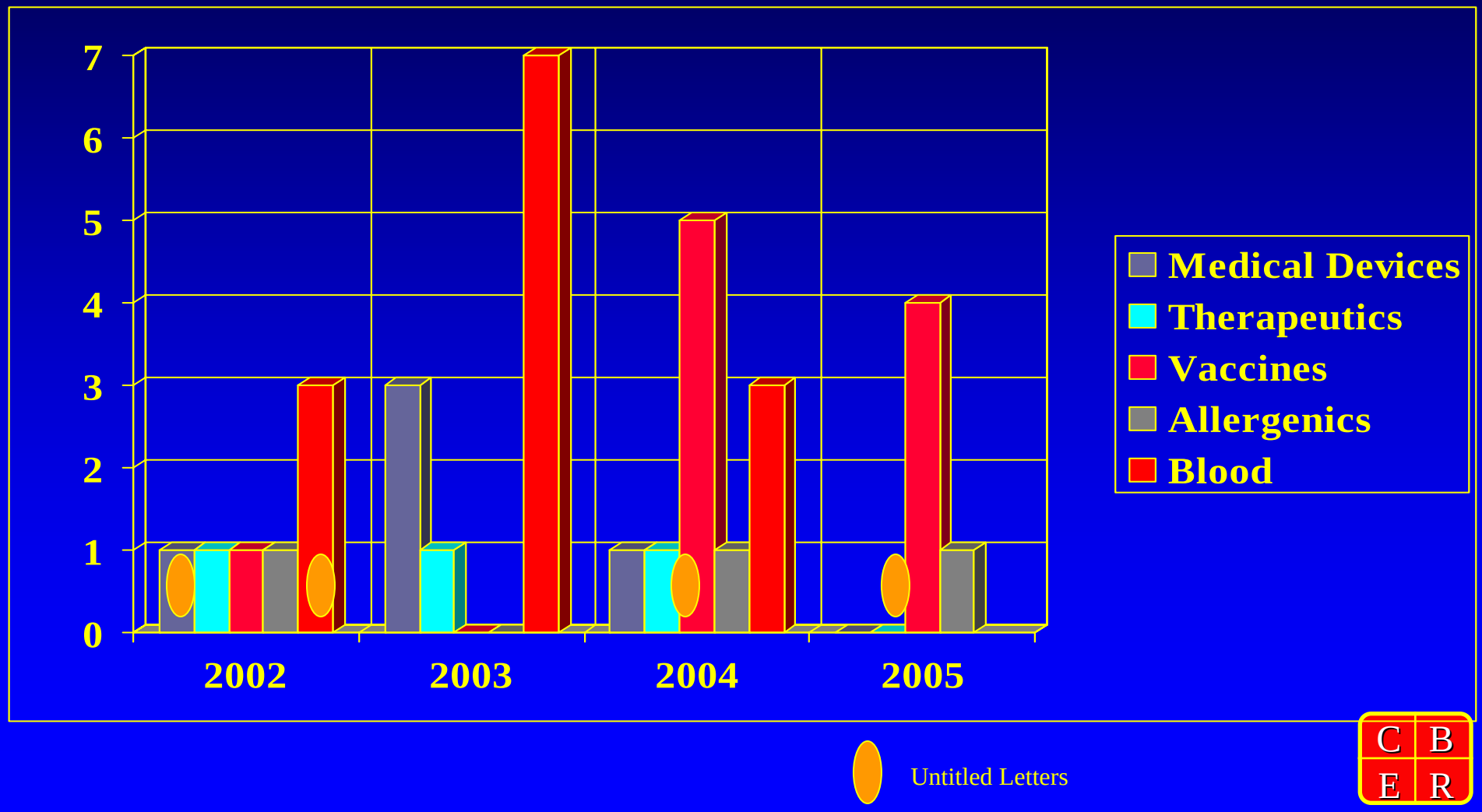
Most Common Violations

- **Blood and plasma**
  - **Failure to follow SOPs [21 CFR 211.100(b)/606.100(b)]**
  - **Inadequate quality oversight into investigations [21 CFR 211.192/606.100(c)]**
- **HCT/Ps – New regulations in Part 1271 effective May 25, 2005, under Part 1270:**
  - **Failure to validate processes to prevent contamination and cross-contamination [21 CFR 1270.31(d)]**

GMP
Biologic Drugs, Devices and Blood



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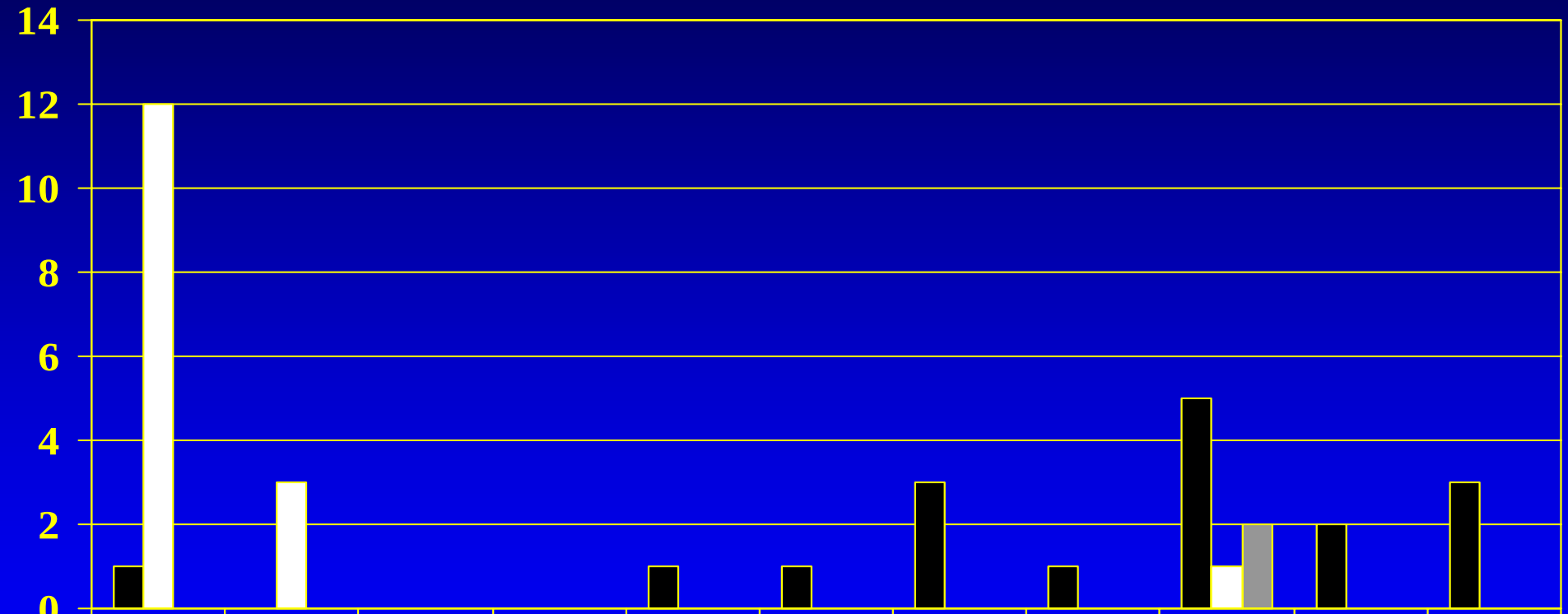
HCT/P Actions
(Since December 1993)



	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02	FY03	FY04
WL's	1	0	0	0	1	1	3	1	5	2	3
Orders	12	3	0	0	0	0	0	0	1	0	0
Other*	0	0	0	0	0	0	0	0	2	0	0

What constitutes an adequate response to a Warning Letter?

- Somewhat dependent on type of violations; however, universally:
  - Should be timely and thorough but realistic
    - Timeframes for corrections should be attainable
  - Should address issues globally
    - Go beyond the specific examples and look at systems (e.g. quality oversight)
    - Should address other locations, products, buildings

In addition:

- An adequate response:
  - Makes scientific sense
  - Includes corrective and preventive action plan and timeframes for completion
  - References any procedural changes and necessary training/retraining
  - Includes documentation to support (e.g. revised SOPs/forms/training records/other records/ validation protocols

What if you disagree with an item?

- **Submit:**
  - **A detailed explanation with documentation/references to support position.**
- **Keep in mind that correction of a violation during or subsequent to the inspection does not preclude a Warning letter citing the violation.**
- **However; prompt, adequate correction, including impact on distributed product, is always considered during the deliberative process.**

Specific issues: Advertising and Promotional Labeling

- Agreement to cease dissemination of identified, violative materials.
- Analysis of other materials to ensure not violative and, if other such materials exist, plan for discontinuation
- Plan to correct misinformation, i.e. dissemination of correct information to those that received violative material

Specific issues: Biological Drugs/Devices

- **Impact on distributed product**
  - **Should you recall product because of the violations?**
  - **Should you report to FDA because of violations? e.g.**
    - **Biological Product Deviation report 21 CFR 600.14**
    - **Medical Device Reporting 21 CFR 800.3**
  - **Should you cease manufacturing/distribution until corrective actions realized?**

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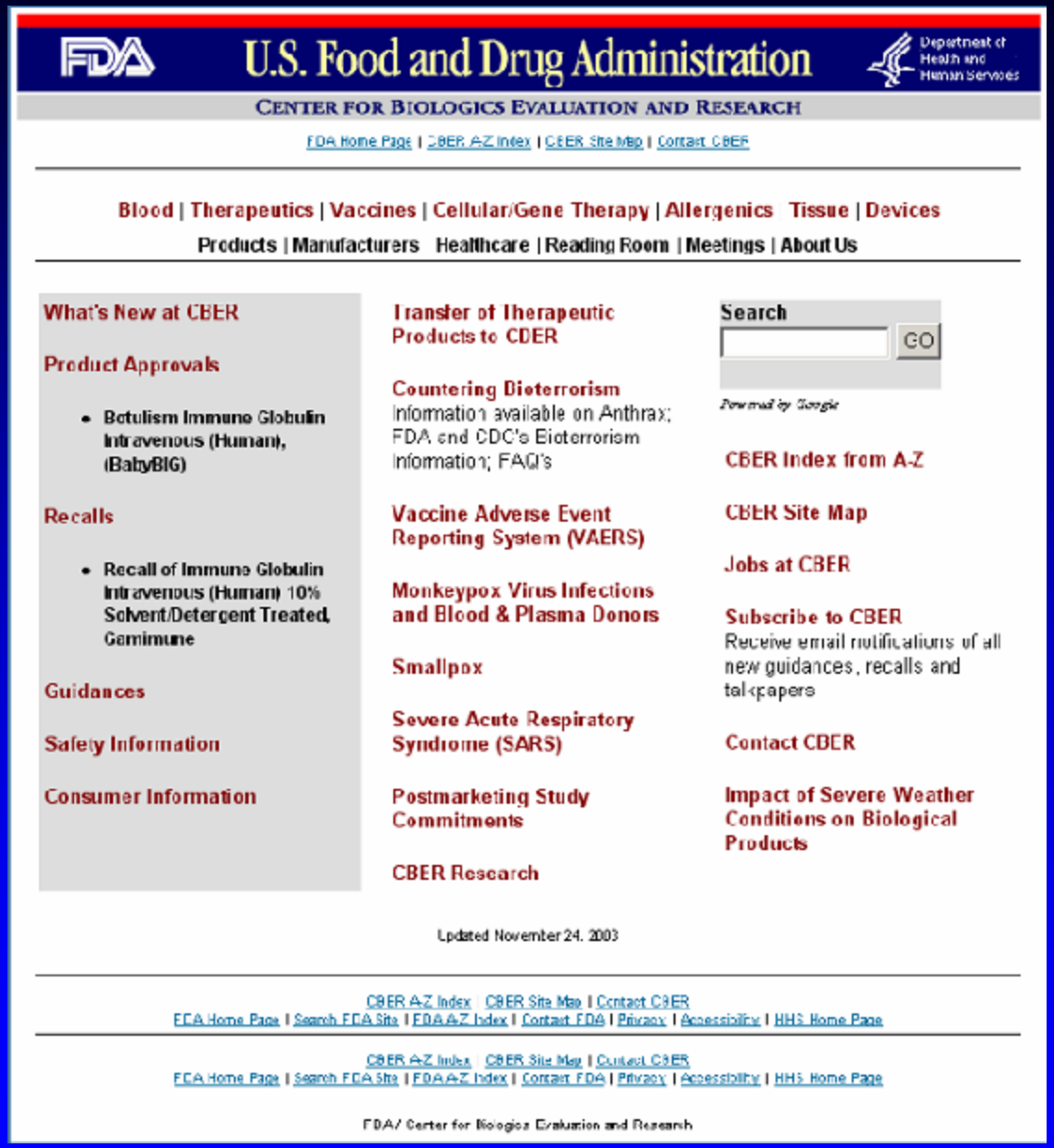
Specific Issues: Internet

Possible corrective actions:

- **Removal of ability to purchase in the United States**
- **Statement – “Not for Sale in U.S.”**
- **Removal of site**



FDA U.S. Food and Drug Administration

Department of Health and Human Services

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What's New at CBER

Product Approvals

- Botulism Immune Globulin Intravenous (Human), (BabyBIG)

Recalls

- Recall of Immune Globulin Intravenous (Human) 10% Solvent/Detergent Treated, Gamimune

Guidances

Safety Information

Consumer Information

Transfer of Therapeutic Products to CDER

Countering Bioterrorism
Information available on Anthrax; FDA and CDC's Bioterrorism information; FAQ's

Vaccine Adverse Event Reporting System (VAERS)

Monkeypox Virus Infections and Blood & Plasma Donors

Smallpox

Severe Acute Respiratory Syndrome (SARS)

Postmarketing Study Commitments

CBER Research

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Impact of Severe Weather Conditions on Biological Products

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We're Here to Help You!

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